Outcome of Art 5(3) procedure - Product Information

(for dexamethasone only-containing oral or IV medicinal products)

[The product information may be amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below]

A. Summary of Product Characteristics

[…]

Section 4.1 – Therapeutic indications

[…]

<Invented name> is indicated in the treatment of coronavirus disease 2019 (COVID-19) in adult and adolescent patients (aged 12 years and older with body weight at least 40 kg) who require supplemental oxygen therapy.

[…]

Section 4.2 – Posology and methods of Administration

[…]

For the treatment of Covid-19

Adult patients 6 mg IV or PO, once a day for up to 10 days.

Paediatric population

Paediatric patients (adolescents aged 12 years and older) are recommended to take 6mg/dose IV or PO once a day for up to 10 days.

Duration of treatment should be guided by clinical response and individual patient requirements.

Elderly, renal impairment, hepatic impairment

No dose adjustment is needed.

[…]

Section 4.4 – Special warnings and precautions for use

[…]

Systemic corticosteroids should not be stopped for patients who are already treated with systemic (oral) corticosteroids for other reasons (e.g. patients with chronic obstructive pulmonary disease) but not requiring supplemental oxygen.

[…]

Section 5.1 - Pharmacodynamic properties

[…]

The RECOVERY trial (Randomised Evaluation of COVid-19 thERapY,)[1] is an investigator-initiated, individually randomised, controlled, open-label, adaptive platform trial to evaluate the effects of potential treatments in patients hospitalised with COVID-19.

The trial was conducted at 176 hospital organizations in the United Kingdom.

There were 6425 Patients randomised to receive either dexamethasone (2104 patients) or usual care alone (4321 patients). 89% of the patients had laboratory-confirmed SARS-CoV-2 infection.

At randomization, 16% of patients were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 60% were receiving oxygen only (with or without non invasive ventilation), and 24% were receiving neither.

The mean age of patients was 66.1+/-15.7 years. 36% of the patients were female. 24% of patients had a history of diabetes, 27% of heart disease and 21% of chronic lung disease.

Primary endpoint

Mortality at 28 days was significantly lower in the dexamethasone group than in the usual care group, with deaths reported in 482 of 2104 patients (22.9%) and in 1110 of 4321 patients (25.7%), respectively (rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001).

In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and in those receiving supplementary oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94).

There was no clear effect of dexamethasone among patients who were not receiving any respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55).

Secondary endpoints

Patients in the dexamethasone group had a shorter duration of hospitalization than those in the usual care group (median, 12 days vs. 13 days) and a greater probability of discharge alive within 28 days (rate ratio, 1.10; 95% CI, 1.03 to 1.17).

In line with the primary endpoint the greatest effect regarding discharge within 28 days was seen among patients who were receiving invasive mechanical ventilation at randomization (rate ratio 1.48; 95% CI 1.16, 1.90), followed by oxygen only (rate ratio, 1.15 ;95% CI 1.06-1.24) with no beneficial effect in patients not receiving oxygen (rate ratio, 0.96 ; 95% CI 0.85-1.08).

Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
	no./total no. of patients (%)		
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	456/1780 (25.6)	994/3638 (27.3)	0.92 (0.84–1.01)
Invasive mechanical ventilation	102/1780 (5.7)	285/3638 (7.8)	0.77 (0.62–0.95)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)

* Rate ratios have been adjusted for age with respect to the outcomes of 28-day mortality and hospital discharge. Risk ratios have been adjusted for age with respect to the outcome of receipt of invasive mechanical ventilation or death and its subcomponents.
† Excluded from this category are patients who were receiving invasive mechanical ventilation at randomization.
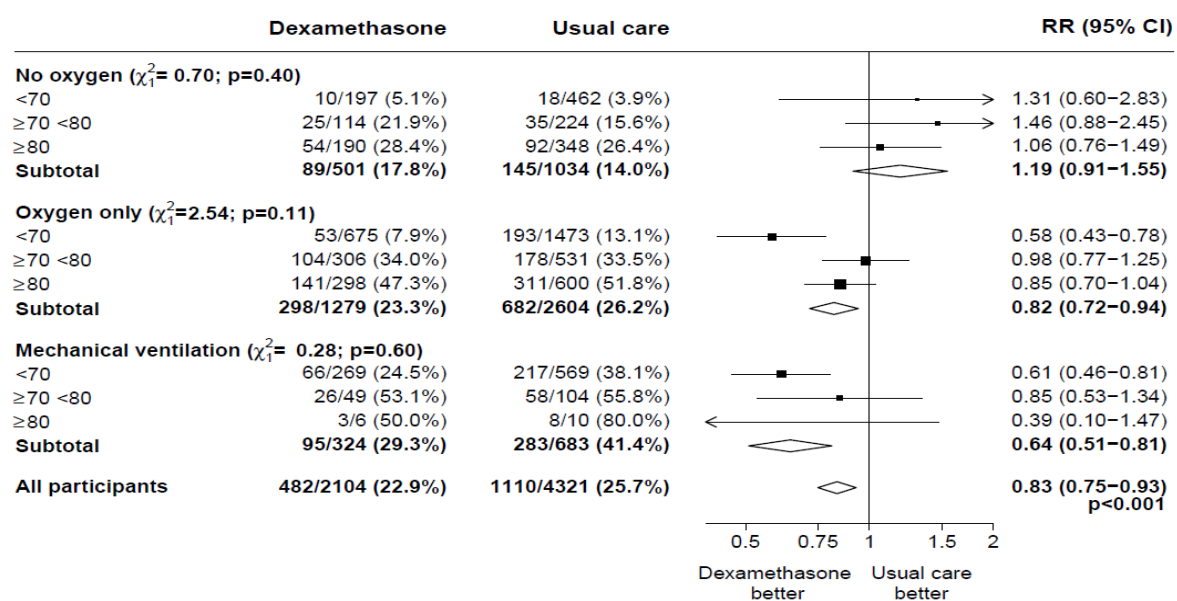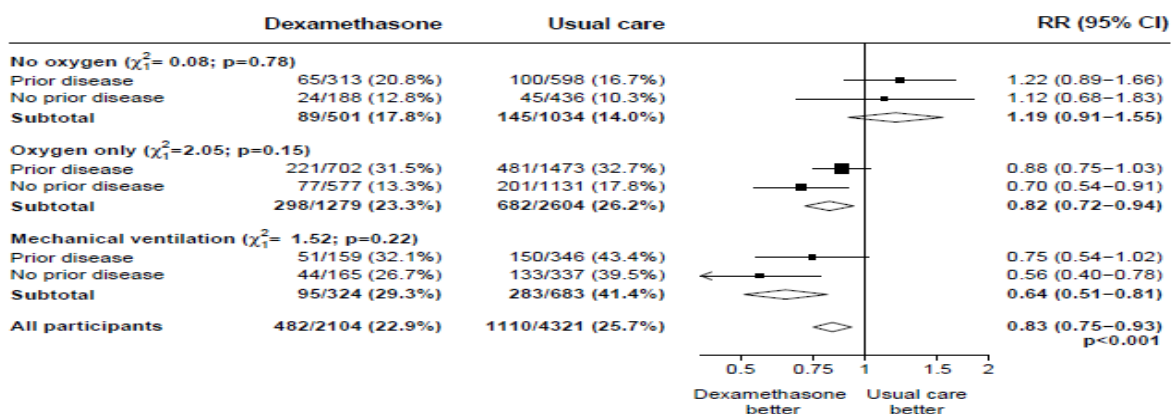
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[1] www.recoverytrial.net

Safety

There were four serious adverse events (SAEs) related to study treatment: two SAEs of hyperglycaemia, one SAE of steroid-induced psychosis and one SAE of an upper gastrointestinal bleed. All events resolved.

Subgroup analyses

Effects of allocation to DEXAMETHASONE on 28–day mortality, by age and respiratory support received at randomisation[2]

	Dexamethasone	Usual care		RR (95% CI)
No oxygen (χ^2_1= 0.70; p=0.40)				
<70	10/197 (5.1%)	18/462 (3.9%)		1.31 (0.60–2.83)
≥70 <80	25/114 (21.9%)	35/224 (15.6%)		1.46 (0.88–2.45)
≥80	54/190 (28.4%)	92/348 (26.4%)		1.06 (0.76–1.49)
Subtotal	**89/501 (17.8%)**	**145/1034 (14.0%)**		**1.19 (0.91–1.55)**
Oxygen only (χ^2_1=2.54; p=0.11)				
<70	53/675 (7.9%)	193/1473 (13.1%)		0.58 (0.43–0.78)
≥70 <80	104/306 (34.0%)	178/531 (33.5%)		0.98 (0.77–1.25)
≥80	141/298 (47.3%)	311/600 (51.8%)		0.85 (0.70–1.04)
Subtotal	**298/1279 (23.3%)**	**682/2604 (26.2%)**		**0.82 (0.72–0.94)**
Mechanical ventilation (χ^2_1= 0.28; p=0.60)				
<70	66/269 (24.5%)	217/569 (38.1%)		0.61 (0.46–0.81)
≥70 <80	26/49 (53.1%)	58/104 (55.8%)		0.85 (0.53–1.34)
≥80	3/6 (50.0%)	8/10 (80.0%)		0.39 (0.10–1.47)
Subtotal	**95/324 (29.3%)**	**283/683 (41.4%)**		**0.64 (0.51–0.81)**
All participants	**482/2104 (22.9%)**	**1110/4321 (25.7%)**		**0.83 (0.75–0.93)** p<0.001

0.5   0.75   1   1.5   2
Dexamethasone better   Usual care better

Effects of allocation to DEXAMETHASONE on 28–day mortality, by respiratory support received at randomisation and history of any chronic disease.[3]

	Dexamethasone	Usual care		RR (95% CI)
No oxygen (χ^2_1= 0.08; p=0.78)				
Prior disease	65/313 (20.8%)	100/598 (16.7%)		1.22 (0.89–1.66)
No prior disease	24/188 (12.8%)	45/436 (10.3%)		1.12 (0.68–1.83)
Subtotal	89/501 (17.8%)	145/1034 (14.0%)		1.19 (0.91–1.55)
Oxygen only (χ^2_1=2.05; p=0.15)				
Prior disease	221/702 (31.5%)	481/1473 (32.7%)		0.88 (0.75–1.03)
No prior disease	77/577 (13.3%)	201/1131 (17.8%)		0.70 (0.54–0.91)
Subtotal	298/1279 (23.3%)	682/2604 (26.2%)		0.82 (0.72–0.94)
Mechanical ventilation (χ^2_1= 1.52; p=0.22)				
Prior disease	51/159 (32.1%)	150/346 (43.4%)		0.75 (0.54–1.02)
No prior disease	44/165 (26.7%)	133/337 (39.5%)		0.56 (0.40–0.78)
Subtotal	95/324 (29.3%)	283/683 (41.4%)		0.64 (0.51–0.81)
All participants	482/2104 (22.9%)	1110/4321 (25.7%)		0.83 (0.75–0.93) p<0.001

0.5   0.75   1   1.5   2
Dexamethasone better   Usual care better

[2, 3] (source: Horby P. et al., 2020; https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1 ; doi: https://doi.org/10.1101/2020.06.22.20137273)

Package Leaflet

1. **What <invented name> is and what it is used for**

Dexamethasone is a synthetic glucocorticoid (adrenocortical hormone)

[…]

<invented name> is used as a treatment of coronavirus disease 2019 (COVID-19) in adult and adolescent patients (aged 12 years and older with body weight at least 40 kg) with difficulty breathing and need of oxygen therapy.

[…]

2. **What you need to know before you <take> <use> <invented name>**

[…]

You should not stop taking any other steroid medications unless your doctor has instructed you to do.

Talk to your doctor, pharmacist or nurse before you take <invented name>.

General precautions regarding steroid use in specific diseases, masking infection, concomitant medicines etc. in line with current recommendations.

[…]

3. **How to <take> <use> <invented name>**

[…]

Take <invented name> as only as prescribed by your doctor. Your doctor will decide how long you should take dexamethasone for. Check with your doctor or pharmacist if you are not sure.

For the treatment of Covid-19

Adult patients are recommended to <take> <be given> *[PO or IV; amend to specific formulation, as appropriate]* 6 mg once a day for up to 10 days.

Use in adolescents

Paediatric patients (adolescents of 12 years of age or older) are recommended to <take> <be given> *[PO or IV amend to specific formulation, as appropriate]* 6 mg once a day for up to 10 days.

[…]